Examination of Reduced Volume aPCC (activated Prothrombin Complex Concentrate [FEIBA]) for Accelerated Infusion in Adult Hemophilia A or B Patients With Inhibitors: FEIBA STAR

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INTRODUCTION

- Development of inhibitory antibodies to Factor VIII or Factor IX replacement therapy currently represents the most serious complication of hemophilia treatment.[1]
- The presence of inhibitors makes response to treatment more challenging, and patients with inhibitors have an increased risk of experiencing difficult-to-control bleeds that can cause life- and limb-threatening joint, muscle, and deep tissue bleeding.[2]
- Use of bypassing agents such as activated prothrombin complex concentrate (aPCC: FEIBA) or rFVIIa has significantly improved treatment of hemophilia A and B patients with inhibitors.[3]
- Prophylaxis with FEIBA in adults[4] and children[5] is effective in preventing and decreasing the number of overall bleeds, target joint bleeds, and hemarthrosis.
- A crucial success factor for continued benefit of FEIBA prophylaxis in inhibitor patients is adherence to the prescribed regimen. Therefore, the time taken to infuse a product is an important consideration.
- A recent study of real world FEIBA use (FEIBA PASS) showed patients infused faster (mean infusion rate = 3.7 U/kg/min, min-max range 0.9-23.5) than currently indicated in the FEIBA SPC (2 U/kg/min).[6]
- A study (FEIBA STAR) is underway to examine the safety of reducing the time of infusion even further through reduced volume and increased infusion rate of FEIBA in hemophilia A or B patients with inhibitors.
  - EudraCT Number: 2015-005781-39
  - ClinicalTrials.gov: NCT02764489

OBJECTIVE

Here we describe the design of a 2-part, Phase 3b/4, prospective, open-label, multicenter study to be conducted in up to 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 Bethesda units). The purpose of the study is to:

- Compare the pharmacokinetics (PK) and safety of FEIBA (aPCC) reconstituted in a reduced volume of sterile water for injection (SWFI) versus regular volume SWFI, administered at the standard infusion rate of 2 U/kg/min
- Evaluate the safety of infusing 50% reduced volume FEIBA at increased rates of 4 and 10 U/kg/min

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STUDY DESIGN

Treatment

The study is divided into 2 parts.

- In Part 1, subjects will receive 6 infusions at a rate of 2 U/kg/min (see Figure 1):
  - Subjects will be randomly assigned (1:1) to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa (infusion 1–3)
  - After a washout period of at least 12 days following the third infusion, subjects will crossover to the next treatment group (infusion 4–6)
  - Infusions 1 and 4 will be for PK and safety analysis; infusions 2, 3, 5, and 6 will be for collection of additional safety data
- Part 2 is non-randomized with sequential enrollment of subjects who complete Part 1. In this part of the study, all subjects will receive 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI at 4 U/kg/min followed by 3 infusions of FEIBA at reduced volume at a rate of 10 U/kg/min (see Figure 2):
  - FEIBA infusions 7, 8 ,and 9 will be administered at 4 U/kg/min rate. The infusions will be administered every 48 hours to allow time to monitor safety and tolerability of the higher infusion rate
  - Subjects will follow with 3 infusions (infusion 10, 11, 12) of FEIBA at 10 U/kg/min rate. Again, infusions will be administered every 48 hours.
  - Following the last infusion, a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion.

Outcome Measures

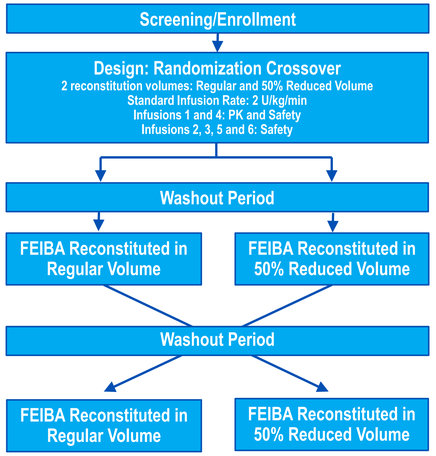
- Primary Outcome Measures
  - $AUC_{0\text{-}216h}$ of FEIBA component Factor II (FII) in subjects
  - Occurrence of thromboembolic and allergic type hypersensitivity reactions
- Secondary Outcome Measures

  Efficacy/PK
  - Incremental recovery of FEIBA component FII in subjects
  - $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, and t_{max} of FEIBA component FII in subjects

  Safety

  Evaluate occurrence of:
  - All AEs and SAEs
  - AEs leading to discontinuation
  - Infusion site reactions
  - All AEs occurring within 24 to 72 hours of Investigational Product (IP) infusion
  - Thrombotic markers
  - Vital signs and clinical laboratory assessments

Figure 1: Study Design for Part 1



Patients

- Up to 24 adult subjects (age ≥ 18 to ≤ 65 years) with hemophilia A or B with inhibitors of any severity
- All subjects will have a documented history of inhibitors requiring the use of bypassing agents (FEIBA or rFVIIa)

Inclusion and Exclusion Criteria

- Patients are eligible for inclusion in the study if they:
  - Are hepatitis C virus (HCV) negative or HCV positive with stable hepatic disease
  - Are human immunodeficiency virus (HIV) negative or HIV positive with stable disease and a cluster of differentiation 4 (CD4) count ≥ 200 cell/mm^3
  - Have negative blood pregnancy test and agree to employ adequate birth control measures, or are of non-childbearing potential
- Patients are excluded from the study if they have:
  - Known hypersensitivity to FEIBA or any of its components
  - Clinically symptomatic liver disease
  - Clinical or laboratory evidence of disseminated intravascular coagulation
  - Prior history or evidence of thromboembolic event, or diagnosis of diseases that may increase the subject's risk of thromboembolic complications
  - Platelet count < 100,000/µL
  - Other condition that will affect patient safety & compliance

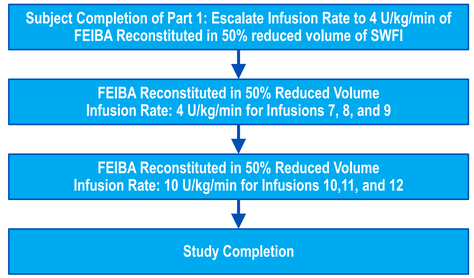
Planned Duration of Subject Participation

- First subject in is planned for September 2016;-each subject will spend approximately 60-90 days in the study. Last subject in is planned for Q4 2017.
- The study will be completed in Q2 2018.

Study Ethics

- Before enrollment of patients into this study, the ethics committee and applicable regulatory authorities will approve this study
- All patients will be required to provide informed consent prior to study enrollment
- This study will be monitored by an Internal Safety Monitoring Committee (ISMC); all SAEs will be reviewed in real time by the Chair of the ISMC.
- There are 3 planned ISMC meetings:
  - At least 48 hours after 6 subjects in Part 1 have completed infusion 5
  - At least 48 hours after 6 subjects have completed infusion 8 (Part 2)
  - At least 48 hours after 6 subjects have completed infusion 11 (Part 2)

Figure 2: Study Design for Part 2



CONCLUSION

Prophylaxis with aPCC in current practice leads to improved outcomes in patients with inhibitors.

The possibility of reducing infusion volumes and accelerating infusion rates may lead to increased adherence to FEIBA prophylaxis and associated improved outcomes.

REFERENCES

1. Leissinger CA. Prevention of bleeds in hemophilia patients with inhibitors: emerging data and clinical direction. *Am J Hematol.* 2004;77:187-193.
2. Konkle BA, Ebbesen LS, Erhardtsen E, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost.* 2007;5:1904-1913.
3. Sjamsoedin LJ, Heijnen L, Mauser-Bunschoten EP, et al. The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII. A double-blind clinical trial. *N Engl J Med.* 1981; 305 (13): 717-21.
4. Antunes SV, Tangada S, Stasyshyn O, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia* 2014; 20 (1): 65-72.
5. Ewing N, Escuriola-Ettingshausen C, Kreuz W. Prophylaxis with FEIBA in paediatric patients with haemophilia A and inhibitors. *Haemophilia* 2015; 21 (3): 358-64.
6. Negrier C, Voisin S, Baghaei F, et al. Global Post-Authorization Safety Surveillance Study: real-world data on prophylaxis and on-demand treatment using FEIBA (an activated prothrombin complex concentrate). *Blood Coagul Fibrinolysis.* 2016.

DISCLOSURES

*All authors are full-time employees of Baxalta, now part of Shire.